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| EXAMINER |
|---|
| SZPERKA, MICHAEL EDWARD |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/651,690 | KIM ET AL. | |
| | Examiner | Art Unit | |
| | Michael Szperka | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-293* is/are pending in the application.

4a) Of the above claim(s) *20-27,41, 42, 70-72,83-85,112, 138,164,176 and 188-276* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19, 28-69, 73-82, 86-137, 139-163, 165-175, 177-187, and 277-293* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/19/04, 7/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's response and amendment filed December 20, 2004 is acknowledged.

Claims 277-293 have been added.

Claims 1-293 are currently pending.

2. Applicant's election without traverse of Group XVII, claims 1-19, 28, 30-36, 38-40, 43-65, 67-69, 73-78, 80-82, 86-111, 139-163, 165-175, 177-187 and new claims 277-293, drawn to a method of treatment for inhibiting spontaneous abortion or implantation failure by using an antibody that binds TNF-α, as well as the election of a method of measuring intracellular cytokine levels and the specific TH1 cytokine TNF-α and the specific Th2 cytokine IL-10 in the reply filed on December 10, 2004 is acknowledged. Upon examination of the prior art, the examiner has decided to withdraw the restriction requirement between the elected Group and Groups XIV and XVIII. The other groups are drawn, respectively, to methods of treatment for inhibiting spontaneous abortion or implantation failure by administering an antibody specific for INF-γ or by administering a soluble TNF-α receptor. As such, the rejoined Group being examined includes claims 1-19, 28-40, 43-69, 73-82, 86-111, 113-137, 139-163, 165-175, 177-187 and new claims 277-293. The art examination of methods of measuring cytokines and the cytokines elected to be measured have been extended beyond the elected species.

3. Claims 20-27, 41, 42, 70-72, 83-85, 112, 138, 164, 176, and 188-276 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 20, 2004.

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

***Claim Objections***

5. Claim 82 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Specifically, claim 82 depends from claim 37 and recites the limitation that the TNF-α antagonist is CDP870. Claim 37 recites the limitation that the TNF-α antagonist is etanercept. CDP870 and etanercept are different TNF-α antagonists, and as such claim 82 fails to further limit claim 37.

## *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

7. Claims 1-19, 28-40, 43-52 and 277 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Omitted steps include how the patient's Th1 to Th2 ratio is measured. Specifically, how is the ratio determined? Is the ratio dependent upon the presence/absence of T cells, cytokines, T cells secreting cytokines, or something else entirely?

The claims also omit steps concerning how a patient's Th1 to Th2 ratio is reduced. Specifically, what compounds or treatment regimens are used to cause this effect in the intended patient? How will such compounds be administered? How will the efficacy of the treatment be monitored or determined?

Additional detail concerning some of the above issues can be found in later dependent claims, and as such one potential way to obviate this rejection is to incorporate limitations found in dependent claims into the rejected claims.

8. Claims 38-40, 67-69, 80-82, 139-163, 165-175, 177-187, and 291-293 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38, 67, 80, 139-163, and 291 are indefinite in the recitation of "D2E7" because its characteristics are not known. Similarly claims 39, 68, 81, 165-175, and 292 which recite "CDP571" and claims 40, 69, 82, 177-187, and 293 which recite "CDP870" are also indefinite. The use of "D2E7, CDP571, or CDP870" as the sole means of identifying the claimed TNF-α antagonist renders the claims indefinite because this is merely a laboratory designation which does not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely products.

Amending the claims to recite the appropriate accession numbers from an acceptable biological depository for the hybridomas that secrete these antibodies would be one way to obviate this rejection.

Note that claims reciting infliximab or etanercept have not been held as indefinite since these terms are the accepted generic names for a specifically defined humanized anti-TNF-α antibody and a specifically defined soluble TNFR-Ig construct.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 38-40, 67-69, 80-82, 139-163, 165-175, 177-187, and 291-293 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement

requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed methods require the use of specific TNF-α antagonists identified only as D2E7, CDP571, and CDP870, and it appears that these reagents are particular monoclonal antibodies that neutralize TNF-α. **As a required element, these materials must be known and readily available to the public or obtainable by a repeatable method set forth in the specification.** If they are not so obtainable or available, a deposit of the pertinent hybridoma that produces the claimed antibody may satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See 37 CFR 1.801-1.809.

It is noted that the specification does not appear to provide guidance concerning the production of antibodies that neutralize TNF-α that can be used in methods of treatment. Page 10, lines 1-20, discloses the companies that make the required reagents, but **there are no assurances that these companies will continue to provide access to these products in the future.** The specification does not indicate that these materials have been deposited with a recognized international depository under the terms of the Budapest Treaty or indicate the terms under which such deposits were made.

If such deposits had been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridomas that secrete D2E7, CDP571, and

CDP870 have been deposited under the Budapest Treaty and that these hybridomas will be irrevocably and without restriction or condition released to the public upon the issuance of a patent **to claims recited in the instant case** would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer. See 37 CFR 1.806 and MPEP 2410-2410.01. If the deposit has not been made under the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the vector described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1, 12-15, 28-31, 33, 35, 43, 44, 49, 53, 56, 61, and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaouat et al. (J. Immunol., 1995, 154:4261-4268, see entire document).

Chaouat et al. disclose multiple methods that increase the number of successful pregnancies in the CBA x DBA/2 mouse strain that is significantly prone to spontaneous abortions (also referred to as fetal resorption in the text, see particularly the title and the Materials and Methods subsection Fetal resorption) as compared to CBA x BALB/c controls (see entire document, particularly the abstract). It is disclosed that in normal pregnancies Th2 responses are predominant in comparison to Th1 responses, but that CBA x DBA/2 mice show increased levels of the Th1 cytokines IL-2, INF-$\gamma$, and TNF-$\alpha$ and are deficient in the Th2 cytokines IL-4 and IL-10 relative to control mice (see

particularly the paragraph that spans pages 4261 and 4262, the first full paragraph of page 4262, the first paragraph of the results section on page 4263, and Figure 1). Th1 cytokine responses can be suppressed, and spontaneous abortion can be prevented, in these mice by the administration of recombinant IL-10 protein (which antagonizes the activity of INF-$\gamma$ and TNF-$\alpha$), the administration of a neutralizing monoclonal antibody that binds INF-$\gamma$, the administration of pentoxifillin (a compound that inhibits the production of TNF-$\alpha$, thus making it a TNF-$\alpha$ antagonist) and the administration of recombinant ovine trophoblastin (see particularly Figures 3, 5, 6, the paragraph that spans pages 4263 and 4264, the first two full paragraphs of page 4265 and the last full paragraph of page 4266). The administration of recombinant IL-10 directly enhances the level of Th2 cytokines in the subject. The mice used in the experiments were allowed to mate, and as such they experienced a natural conception (see particularly the Materials and Methods section).

Therefore, the prior art anticipates the claimed invention.

13. Claims 1, 12, 14, 28-32, 35, 43, 44, 49, 53, 56, 61, and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Chaouat (Cell Immunol., 1994, 157:328-340, see entire document).

Chaouat teaches the prevention of embryo resorptions in the spontaneous abortion prone mouse model CBA x DBA/2 through the administration of a neutralizing polyclonal rabbit anti-TNF antiserum and thought the administration of pentoxyfillin, a compound that suppresses the production of TNF (see particularly the abstract, the

second paragraph of the introduction, the paragraph that spans pages 334 and 335, and the second full paragraph on page 338). These treatments are able to suppress the Th1 cytokine TNF-α in these mice. Inhibition of spontaneous abortion inherently enhances birth rates and the ability of an animal to carry an embryo to term. Pregnancy in the experimental mice was determined by the observation of a vaginal plug and as such a natural conception occurred by the mating of the mice. All animals have an immune system, and as such they inherently have a ratio of Th1 to Th2 responses.

Therefore, the prior art anticipates the claimed invention.

14. Claims 1, 12, 14, 28-30, 31, 33-39, 43-46, 49, 53, 56-58, 61, 65-68, 73, 76-81, 86, 89-91, 94, 98-100, 113, 116-118, 121, 125-126, 139, 142-44, 147, 151-153, 165, 168-170, 173, and 174 are rejected under 35 U.S.C. 102(e) as being anticipated by Pluenneke (US 2001/0021380 A1, see entire document).

Pluenneke discloses the use of agents that inhibit the activity or production of TNF-α in the treatment of many medical disorders (see entire document, particularly the abstract and paragraphs 8 and 9). Examples of TNF-α inhibiting agents that are useful in the methods disclosed by Pluenneke include the TNFR-Ig construct etanercept, as well as anti-TNF-α monoclonal antibodies including, but not limited to, infliximab, D2E7, and CDP571 (see particularly paragraphs 19, 20, and 32). These reagents are to be used in treating disorders of the female reproductive system and include multiple implant failure/infertility and spontaneous abortion (see particularly paragraph 73). It should be noted that methods that inhibit spontaneous abortion or infertility inherently

enhance the ability of a subject to carry an embryo to term. Suitable dosages and routes of administration for the reagents disclosed by Pluenneke are provided (see particularly paragraphs 26-32). The disclosed dosage ranges for etanercept and the anti-TNF-α monoclonal antibodies overlap with the ranges claimed by applicant, and these agents can be injected intravenously, intramuscularly, subcutaneously, or can be administered as aerosols, eyedrops, oral medications including pills, or topical forms such as lotions, gels, sprays or ointments (see particularly paragraph 26). Patient populations included for treatment using the methods and compositions of Pluenneke include both humans and non-human animals (see particularly paragraph 81).

Base claim 1 recites the limitation that a subject have a Th1 to Th2 ratio, but the above indicated claims that depend from this base claim do not introduce the further limitation that this ratio must be measured. Animals have immune systems, and as such they will all have a population of Th1 and Th2 cells, and thus they also have an inherent Th1 to Th2 ratio. Applicant's claims modify this ratio by introducing Th1 cytokine antagonists. The teachings of Pluenneke provide methods and compositions to antagonize the Th1 cytokine TNF-α, and as such these methods inherently alter the Th1 to Th2 ratio present in the subject being treated.

Therefore, the prior art anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1, 12, 28, 35, 37, 40, 53, 69, 73, 82, 177, 180-183, and 186 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Athwal et al. (US 2002/0151682 A1, see entire document).

The teachings of Pluenneke have been discussed above. These teachings differ from the claimed invention in that Pluenneke does not disclose the anti-TNF-α monoclonal antibody CDP870 as part of his non-limiting examples of anti-TNF-α

antibodies that are suitable for use in his methods of treating infertility and spontaneous abortion.

Athwal et al. disclose the creation of the anti-TNF-α antibody CDP870 (see entire document, particularly Figure 22 and paragraphs 231-266). This antibody is capable of neutralizing TNF-α and is comparable in efficacy to etanercept (see particularly paragraph 262). CDP870 is disclosed as being PEGylated, and as such it has a long plasma half life that is desirable for the treatment of patients (see particularly paragraphs 67 and 26).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody of Athwal et al. for the anti-TNF-α reagents, such as etanercept, used in the methods of Pluenneke. Motivation to make this substitution comes from the teachings of Athwal et al. that increased plasma half life of a reagent is desirable for treating patients and that CDP870 is PEGylated to increase its plasma half life. Therefore, a person of ordinary skill in the art would have been motivated to use CDP870 in the methods of Pluenneke et al. since CDP870 has a comparable efficacy to etanercept, and since CDP870 has the advantage of being PEGlylated to increase its half life, thus making CDP870 an ideal reagent for treating patients as taught by Athwal et al.

Claim 37 is included in this rejection because claim 82 currently depends from claim 37. Based upon the other claims it appears that claim 82 should be dependent upon claim 73. Both claims 73 and 37 are methods of treatment using TNF-α

antagonists, and as such both claims have been included in this rejection since either dependency could be correct.

17. Claims 86, 103-111,113, 129-137, 139, and 155-163 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Coulam et al. (Am J Reproductive Immunol, 1997, 38:57-74, see entire document) as evidenced by Janeway et al. (Immunobiology, Third edition, 1997, pages 3.2-3.3).

The teachings of Pluenneke have been discussed above. These teachings differ from the claimed invention in that they do not teach the administration of the TNF-α antagonist prior to conception, or the administration of a TNF-α antagonist combined with lymphocyte immunization, intravenous IgG, anticoagulants or steroids such as prednisone.

Coulam et al. teaches methods and clinical protocols for use in diagnosing and treating patients that suffer from recurrent spontaneous abortions (see entire document, particularly the introduction). These methods include the administration of heparin, aspirin, prednisone, intravenous Ig, and immunization with paternal lymphocytes to treat such patients (see particularly Table IV). The methods of Coulam et al. only specify IVIg and not a specific Ig isotype, but the most abundant isotype in blood plasma is IgG, and as such Coulam et al. inherently teach the administration of IgG to patients (see particularly the paragraph that spans pages 3.2 and 3.3 of Janeway et al. and the paragraph that spans pages 67 to 68 of Coulam et al.). Table IV of Coulam et al.

indicates that many of the therapeutic interventions may or must be initiated before conception, such therapies including the use of aspirin, prednisone, and therapeutic immunization with lymphocytes (see particularly the first full paragraph of page 67 and Table IV). All of these treatments initiated prior to conception are intended to increase the odds that a successful conception and delivery to term will result (see particularly from the middle of the right column of page 66 to the end of the left column of page 67).

Both Pluenneke and Coulam et al. teach methods and composition that treat spontaneous abortion and infertility. As such, "It is *prima facie* obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

It would also have been *prima facie* obvious to a person of ordinary skill in the art to administer just the TNF-$\alpha$ antagonists of Pluenneke prior to conception. A person of ordinary skill in the art would have been motivated to administer just the TNF-$\alpha$ antagonist at this time based upon the teachings of Coulam et al. that many therapeutic interventions are initiated prior to conception in order to increase the odds of achieving a successful conception and pregnancy. Therefore, initiating treatment with a TNF-$\alpha$ antagonist prior to conception would gain the advantage of increasing the probability that the therapeutic intervention would be successful in inhibiting spontaneous abortion or implantation failure.

18. Claims 1, 53, 73, 86, 101, 102, 113, 127, 128, 139, 154, 165, 175, and 277-292 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Terao et al. (US Patent No. 6,013,252, see entire document).

The teachings of Pluenneke have been discussed above. These teachings differ from the claimed invention in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy), into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

19. Claims 177, 187, and 293 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Athwal et al (US 2002/0151682 A1, see entire document) as applied to claims 1, 12, 28, 35, 37, 40, 53, 69, 73, 82, 177, 180-183, and 186 above, and further in view of Terao et al. (US Patent No. 6,013,252, see entire document).

The teachings of Pluenneke in conjunction with Athwal et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 187 and 293 in that while they do teach TNF-α antagonists in a gel form for administration to a patient, they do not teach the administration of the TNF-α antagonist vaginally.

Terao et al. teach that compounds useful for promoting conception should be administered as an ointment, cream, gel or vaginal suppository (see particularly the paragraph that spans columns 6 and 7, the final paragraph of column 8 and Example 3. Such formulations offer the advantage of being easily administered to the patient (see particularly the paragraph that spans columns 6 and 7).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the TNF-α inhibitors of Pluenneke and Athwal et al. that are used in methods of inhibiting spontaneous abortion or infertility, (which are also methods that promote conception and the maintenance of pregnancy), into a gel for vaginal delivery of the agent. Motivation to make this modification comes from the teachings of Terao et al. that gels or other form that can be applied vaginally offer the advantage of being easily administered to the patient.

20. Claims 1, 5, 6, 12, 14, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed May 19, 2004, see entire document).

The teachings of Pluenneke have been discussed above. In summary, these teachings indicate that all women suffering from disorders of the female reproductive system such as multiple implant failure/infertility and spontaneous abortion should be treated with TNF-$\alpha$ antagonists. These teachings differ from the claimed invention in that they do not disclose the measurement of the Th1 to Th2 ratio in patients being treated for spontaneous abortions or infertility.

Raghupathy et al. teach that significantly greater levels of the Th2 cytokines IL-6 and IL-10 were found in normal pregnancy as compared to women with a history of unexplained recurrent spontaneous abortions (RSA), and that significantly higher levels of the Th1 cytokine IFN-$\gamma$ were found in RSA as compared to normal pregnancy (see entire document, particularly the abstract). Raghupathy et al. calculated the ratio of Th2 to Th1 cytokines because the ratio of these cytokines is more important than their mere presence or absence (see particularly the left column of page 125, the first full paragraph of the left column of page 127, and Table 1). Their data demonstrates a distinctly increased Th2 bias in normal pregnancy and an increased Th1 bias in RSA (see particularly the first full paragraph of the left column of page 127). The cytokines measured by Raghupathy et al. include the Th2 cytokines IL-4, IL-5, IL-6, IL-10, and the

Th1 cytokines IL-2, IFN-γ, TNF-β and TNF-α (see particularly the section titled Cytokine profiles in MLPR on page 124). One particular ratio calculated by Raghupathy et al. was IL-10:TNF-α, although ratios comparing any of the cytokines measured by Raghupathy would have been obvious to calculate (see particularly Table 1). These cytokines are disclosed as having been measured from PBMC stimulated *in vitro* with either irradiated placental cells (MLPR) or soluble antigen (see particularly the materials and methods section) or alternatively, the cytokines were measured directly from patient sera (see particularly the first full paragraph of page 129). Serum cytokine measurements indicated significantly increased IL-6 and IL-10 levels in normal pregnancy as compared to RSA, with significantly increased TNF-α detected in serum from recurrent aborters (see particularly the first full paragraph of page 129).

Raghupathy et al. further teach that appropriate interventions that shift the ratio of immune reactivity toward Th2 dominance or that inhibit Th1 cytokine production are to be administered to patients to help them achieve a successful pregnancy, and that not all women suffering from RSA demonstrate an immunological etiology such as an increased level of Th1 cytokines (see particularly the last two paragraphs of page 129). As such, the identification of patients that have altered cytokine ratios would allow for the more efficacious targeting of immunological therapeutic interventions to only the subset of patients who are likely to be responsive to such interventions (see particularly the last two paragraphs of page 129).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure the Th1 to Th2 ratio of patients as

taught by Raghupathy et al. before performing the therapeutic methods of Pluenneke. Motivation to incorporate this method step comes from the teachings of Raghupathy et al. that not all cases of spontaneous abortion have an immunological etiology, but in those cases that do, therapeutic methods designed to alter the Th1 to Th2 ratio are useful in helping such women achieve a successful pregnancy. As such, incorporation of a screening method to identify women that suffer spontaneous abortion of immunological etiology into the treatment method taught by Pluenneke would offer the advantage of targeting immunotherapy to only those patients that are likely to benefit from such interventions.

21. Claims 1, 2-4, 7-9, 46-48, 50-55, 58-60, 62-64, 73-75, 86-88, 91-93, 95-97, 113-115, 118-120, 122-124, 139-141, 144-146, 148-150, 165-167, and 170-172 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed 5/19/2004, see entire document) as applied to claims 1, 5, 6, 12, 14, and 16-19 above, and further in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document).

The teachings of Pluenneke and Raghupathy et al. have been discussed above. These teachings differ from the claimed invention as recited in claims 2-4, 7-9, 46-48, 50-55, 58-60, 62-64, 73-75, 86-88, 91-93, 95-97, 113-115, 118-120, 122-124, 139-141,

144-146, 148-150, 165-167, and 170-172 in that they do not disclose measuring the Th1 to Th2 cytokine ration using absolute cell counts or by intracellular cytokine staining. These teachings also do not indicate the treatment of the patients that have undergone assisted reproductive technologies such as *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-$\alpha$ expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al.

include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute the cytokine detection methods and patient populations taught by Ng et al. for the detection methods and patients taught collectively by the teachings of Pluenneke and Raghupathy et al. Motivation to make these substitutions comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio. A person of ordinary skill in the art would also have been motivated at the time the invention was made to reduce the absolute counts of CD3+/CD4+ T cells that express TNF-α since this population was shown by Ng et al. to be increased in patients that suffer spontaneous abortions and implantation failure, and the teachings of Pluenneke that methods that suppress the expression of TNF-α are to be used in treating conditions mediated by increased levels of TNF-α, such conditions including multiple implant failure/infertility and spontaneous abortion.

22. Claims 177-179, 182, 184, and 185 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pluenneke (US 2001/0021380 A1, see entire document) in view of Athwal et al (US 2002/0151682 A1, see entire document) and in view of Raghupathy et al. (Cellular Immunology, 196:122-130, of record on form 1449 filed 5/19/2004, see entire document) as applied to claims 1, 5, 6, 12, 14, and 16-19 above, and in view of Ng et al. (Am. J. Reproductive Immunol., 2002, 48:77-86, Presented at the ASRI XXIst Annual Meeting in Chicago, June 9-12 2001, of record on PTO form 1449 filed May 19, 2004) as evidenced by Alak et al. (US patent No. 5,693,534, see entire document).

The teachings of Pluenneke, Athwal et al. and Raghupathy et al. have been discussed above. These teachings differ from the claimed invention in that they do not disclose measuring the Th1 to Th2 cytokine ration using absolute cell counts or by intracellular cytokine staining. These teachings also do not indicate the treatment of the patients that have undergone assisted reproductive technologies such as *in vitro* fertilization or ovulation induction cycles.

Ng et al. teach that there are changes in both absolute counts of T cells that express Th1 and Th2 cytokines, as well as changes in the ratio of these cytokines, when comparing women diagnosed with recurrent spontaneous abortions or who had multiple implantation failures after *in vitro* fertilization and embryo transfer (IVF/ET) with normal pregnancy controls (see entire document, particularly the abstract). Ovulation induction is a routine part of IVF therapy that increases the number of eggs that are retrieved and available for use in IVF therapy, and as such women that have undergone

IVF have also undergone ovulation induction therapy (see Alak et al., particularly column 5, lines 16-34). The data obtained by Ng et al. was collected by intracellular cytokine staining of PBMC isolated from study participants (see particularly the Materials and Methods section). Ng et al. demonstrated that the absolute T cell counts of TNF-α expressing CD3+/CD4+ T cells were significantly increased in implantation failure patients as compared to normal controls (see particularly the paragraph that spans pages 80 and 81). Ng et al. also disclose that increased Th1/Th2 cytokine ratios were observed in women with recurrent pregnancy losses and multiple implantation failures after IVF/ET as compared with normal controls (see particularly the paragraph that spans the right and left columns of page 78). Cytokine ratios compared by Ng et al. include INF-γ/IL-4, INF-γ/IL-10, TNF-α/IL-4, TNF-α/IL10 (see particularly the final paragraph of the results section on page 82). Of these the ratio of TNF-α to IL-10 appeared most important since patients with implantation failures after IVF/ET had an up-regulated TNF-α level and a down-regulated IL-10 level as compared to controls (see particularly Table III, the first paragraph of the discussion on page 82, the paragraph that spans pages 83-84, and the penultimate paragraph on page 84).

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to substitute the cytokine detection methods and patient populations taught by Ng et al. for the detection methods and patients taught collectively by the teachings of Pluenneke, Athwal et al. and Raghupathy et al. Motivation to make these substitutions comes from Raghupathy et al.'s teachings that it is important to identify women suffering from spontaneous abortion that would benefit

from immunological interventions that alter a woman's Th1 to Th2 ratio, and Ng et al.'s teaching of methods that use intracellular cytokine staining and absolute cell counts to identify additional women, such as those undergoing IVF/ET, that would benefit from interventions that alter the Th1 to Th2 ratio.

23. No claims are allowable.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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